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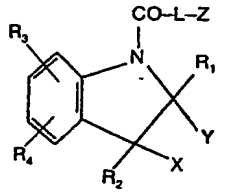
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(54) Indole derivatives having an azabicyclic side chain, process for their preparation, intermediates, and pharmaceutical compositions.

(57) Compounds of formula (I), and pharmaceutically acceptable salts thereof:



(I)

wherein

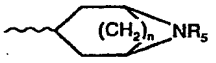
L is NH or O;

X and Y are independently selected from hydrogen or C_{1-4} alkyl, or together are a bond;

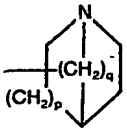
R_1 and R_2 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl-C_{1-4} alkyl, or together are C_{2-4} polymethylene;

R_3 and R_4 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5} polymethylene;

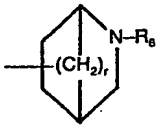
Z is a group of formula (a), (b) or (c)



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl; having 5-HT M-receptor antagonist activity, a process for their preparation and their use as pharmaceuticals.

EP 0 247 266 A1

TITLE MODIFIED
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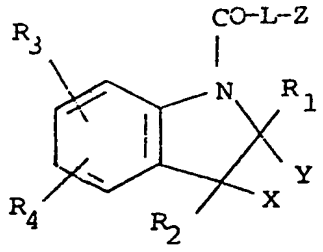
NOVEL COMPOUNDS

This invention relates to novel compounds having useful pharmacological properties, to pharmaceutical compositions containing them, to a process and intermediates for their preparation, and to their use as pharmaceuticals.

GB 2100259A and 2125398A, and EP-A-158265 describe benzoates and benzamides having an azabicyclic side chain and possessing 5-HT antagonist activity.

A class of novel, structurally distinct compounds has now been discovered. These compounds have 5-HT M-receptor antagonist activity, anti-emetic activity and/or gastric motility enhancing activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

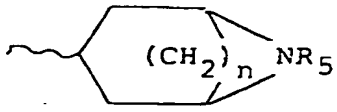
L is NH or O;

X and Y are independently selected from nydrogen or C_{1-4} alkyl, or together are a bond;

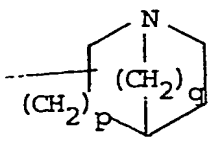
R_1 and R_2 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl-C_{1-4} alkyl, or together are C_{2-4} polymethylene;

R_3 and R_4 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5} polymethylene;

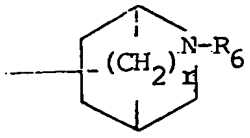
Z is a group of formula (a), (b) or (c)



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl.

Preferably L is NH.

Suitable values for X and Y include hydrogen, methyl, ethyl, n- and iso-propyl; or together are a bond.

Often X and Y are both hydrogen.

Suitable values for R_1 or R_2 include hydrogen, methyl, ethyl, n- and iso-propyl; prop-2-enyl, but-2-enyl, but-3-enyl, 1-methylenepropyl and 1-methylprop-2-yl in their E and Z forms where stereoisomerism exists; or R_1 and R_2 together are as defined in formula (I). Often R_1 and R_2 are both hydrogen.

Values for R_3 and/or R_4 include hydrogen, fluoro, chloro, bromo, CF_3, methyl, ethyl, methoxy, ethoxy, methylthio, ethylthio, acetyl, propionyl, acetylamino, methylsulphonylamino, methylsulphinyl, hydroxy, nitro; and amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-methylamino any of which may be optionally substituted by one or two methyl groups or by a cyclopentyl or cyclohexyl

group or disubstituted by C_4 or C_5 polymethylene; R_3 is often hydrogen and R_4 is hydrogen or a 4-substituent, such as halo or methoxy.

Preferably n is 2 or 3 and p, q and r are 1 or 2.

Examples of R_5/R_6 when C_{1-7} alkyl include as groups of interest C_{1-3} alkyl such as methyl, ethyl and n- and iso-propyl. Within C_{1-7} alkyl, C_{4-7} alkyl are also of interest, especially those of the formula $(CH_2)uR_9$ wherein u is 1 or 2 and R_9 is a secondary or tertiary C_{3-6} alkyl group. Examples of C_{4-7} alkyl include n-, sec- and tert-butyl, n-pentyl, n-heptyl, and iso-butyl, 3-methylbutyl, and tert-butylmethyl.

Examples of R_5/R_6 when C_{3-8} cycloalkyl-C_{1-2} alkyl include in particular those wherein the cycloalkyl moiety is cyclohexyl or cyclopropyl. Examples of include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, tert-butylmethyl, iso-propylmethyl, iso-propylethyl and tert-butylethyl.

R_5/R_6 may in particular be cyclopropylmethyl, cyclohexylmethyl, iso-propylmethyl, tert-butylmethyl or iso-propylethyl, preferably tert-butylmethyl.

Examples of R_5/R_6 when C_{2-7} alkenyl-C_{1-4} alkyl include prop-2-enyl, but-2-enyl, but-3-enyl, 1-methylenepropyl and 1-methyl-prop-2-enyl in their E and Z forms when stereoisomerism exists.

R_5/R_6 is preferably methyl or ethyl, most preferably methyl.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, lactic, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_{10}-T wherein R_{10} is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_{10} include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

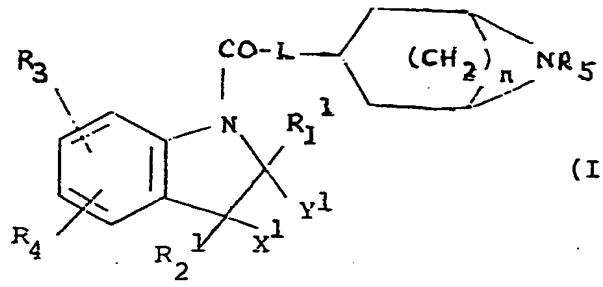
The compounds of formula (I) may also form internal salts such as pharmaceutically acceptable N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

It will also be realised that compounds of formula (I) may adopt an endo or exo configuration with respect to L. The endo configuration is preferred.

A group of compounds within formula (I) is of formula (II):

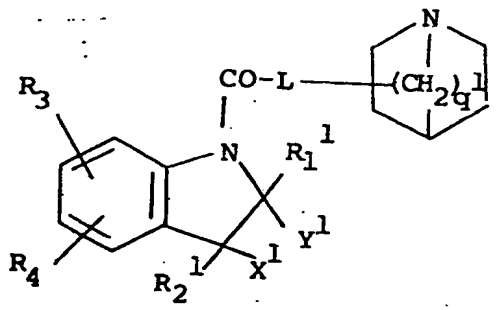


(II)

wherein X^1 and Y^1 are independently hydrogen, methyl or ethyl, or together are a bond, $R_1{}^1$ and $R_2{}^1$ are independently hydrogen, methyl or ethyl and the remaining variables are as defined in formula (I).

Examples of the variables and preferred variables are as so described for corresponding variables in relation to formula (I).

A further group of compounds within formula (I) is of formula (III):

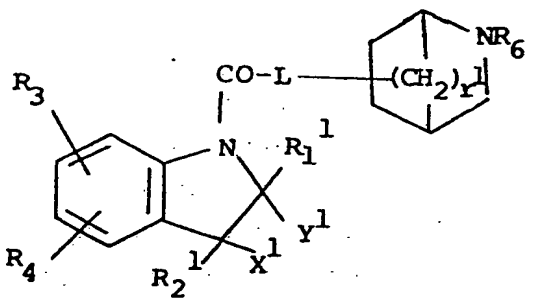


(III)

wherein q^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are as so described for the corresponding variables in formula (I).

There is a further group of compounds within formula (I) of formula (IV):

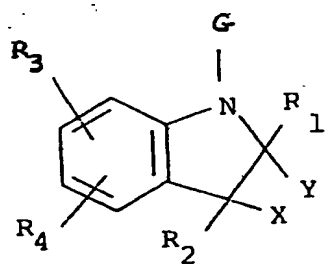


(IV)

wherein r^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are so described as the corresponding variables in formula (I).

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):



(V)

with a compound of formula (VI):

$$J\text{-}Z^1 \qquad \text{(VI)}$$

wherein

G is COQ_1, where Q_1 is a leaving group, or hydrogen; and, when G is COQ_1, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage with the compound of formula (V); Z^1 is Z as defined or wherein R_5/R_6 is replaced by a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting any R_3 and R_4 group to another R_3 and R_4 group respectively, converting Z^1, when other tnan Z, to Z; converting X and Y to other X and Y; and

optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of leaving groups Q_1, displaceable by a nucleophile, include halogen such as chloro and bromo; C_{1-4} alkoxy, such as CH_3O and C_2H_5O-; PhO-; activated hydrocarbyloxy, such as Cl_5C_6O- or Cl_3CO-; succinimidyloxy; and imidazolyloxy. Preferably Q_1 is halogen, most preferably chloro.

If a group Q_1 is a halide or imidazolyloxy, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0-100°C, in particular 10-80°C are suitable.

If a group Q_1 is C_{1-4} alkoxy, phenoxy, activated hydrocarbyloxy or succinimidyloxy then the reaction is preferably carried out in an inert polar solvent, such as toluene or dimethylformamide. In this instance, it is preferred that the group Q_1 is Cl_3CO- or succinimidyloxy and that the reaction is carried out in toluene at reflux temperature.

When J is OH or a reactive derivative thereof, the reactive derivative is often a salt, such as the lithium, sodium or potassium salt.

When G is hydrogen, $J-Z^1$ may be a compound of formula (VII) or (VIII) when L is NH; or of formula (IX) when L is O:

$$O=C=N-Z^1 \qquad \text{(VII)}$$

$$Q_2-\overset{\overset{O}{\|}}{C}-NH-Z^1 \qquad \text{(VIII)}$$

$$Q_3-\overset{\overset{O}{\|}}{C}-O-Z^1 \qquad \text{(IX)}$$

wherein
Z^1 is as hereinbefore defined, and Q_2 and Q_3 are leaving groups, preferably Cl_3CO and Cl respectively.

When $J-Z^1$ is of formula (VII), the reaction is preferably carried out in an inert solvent, under conventional conditions 0-100°C.

Q_2 is a leaving group as defined for Q_1 hereinbefore; and the reaction is carried out in accordance with the conditions described herein for the reaction wherein G is COQ_1.

Examples of Q_3, displaceable by a nucleophile, include halogen, such as chloro and bromo; and activated hydrocarbyloxy, such as Cl_5C_6O- and Cl_3CO.

If a group Q_3 is a halide, the reaction is carried out as described above for Q_1 halide.

If Q_3 is activated hydrocarbyloxy, the reaction is carried out as described for Q_1 activated hydrocarbyloxy.

It will be apparent that compounds of the formula (I) containing an R_3 or R_4 group which is convertible to another R_3 or R_4 group are useful novel intermediates. A number of such conversions is possible not only for the end compounds of formula (I), but also for their intermediates as follows:

(i) a hydrogen substituent is convertible to a nitro substituent by nitration;

(ii) a nitro substituent is convertible to an amino substituent by reduction;

(iii) a C_{1-7} acylamino substituent is convertible to an amino substituent by deacylation;

(iv) an amino substituent is convertible to a C_{1-4} acylamino substituent by acylation with a carboxylic acid derivative;

(v) a hydrogen substituent is convertible to a halogen substituent by halogenation;

(vi) a C_{1-6} alkylthio or C_{1-6} alkylsulphinyl substituent is convertible to a C_{1-6} alkylsulphinyl or a C_{1-6} alkylsulphonyl substituent respectively by oxidation;

(vii) an amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-N-C_{1-4} alkylamino substituent is convertible to a corresponding substituent substituted by one or

two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4} alkyl or phenyl C_{1-4} alkyl groups any of which phenyl groups may be substituted by one or more groups selected from halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy and nitro, or disubstituted by C_{4-5} polymethylene, by N-alkylation;

(viii) an amino substituent is convertible to a C_{1-6} alkylsulphonylamino group or an aminosulphonylamino group optionally N-substituted as defined by acylation with a C_{1-6} alkylsulphonyl chloride or di-substituted aminosulphonyl chloride.

(ix) A C_{1-4} alkylamino substituent group is convertible to a N-(C_{1-6} alkylsulphonyl)N-C_{1-4} alkylamino group or an N-(amino sulphonyl)N-C_{1-4} alkylamino group optionally N-substituted as defined by acylation with a C_{1-6} alkylsulphonyl chloride or di-substituted aminosulphonyl chloride.

Conversions (i) to (ix) are only exemplary and are not exhaustive of the possibilities.

In regard to (i), nitration is carried out in accordance with known procedures.

In regard to (ii), the reduction is carried out with a reagent suitable for reducing nitroanisole to aminoanisole.

In regard to (iii), deacylation is carried out by treatment with a base, such as an alkali metal hydroxide.

In regard to (iv), (viii), and (ix) the acylation is carried out with an acylating agent, such as the corresponding acid or acid chloride. Formylation is carried out with the free acid.

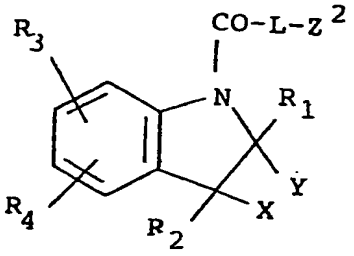
In regard to (v), halogenation is carried out with conventional halogenating agents.

In regard to (vi), oxidation is carried out at below ambient temperatures in a non-aqueous solvent, such as a chlorinated hydrocarbon, in the presence of an organic peracid, such as 3-chloroperbenzoic acid, or in water in the presence of a soluble strong inorganic oxidant, such as an alkali metal permanganate or in aqueous hydrogen peroxide. It will be realised that this process may also N-oxidise the N- moiety of a side chain (a), (b) or (c) and suitable precautions will routinely be taken by those skilled in the art.

In regard to (vii), alkylation is carried out with a corresponding alkylating agent such as the chloride or bromide under conventional conditions.

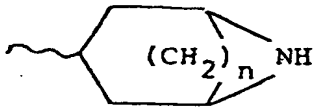
Z^1 when other than Z may have a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups as defined for R_3 and R_4. Such benzyl groups may, for example, be removed, when R_3 or R_4 is not halogen, by conventional transition metal catalysed hydrogenolysis to give compounds of the

formula (X):

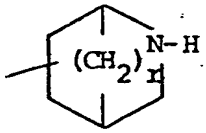


(X)

wherein Z^2 is of formula (d) or (e)



(d)



(e)

wherein the variables are as defined in formula (I).

This invention also provides a further process for the preparation of a compound of the formula (I) which comprises N-alkylating a compound of formula (X), and optionally forming a pharmaceutically acceptable salt, of the resulting compound of the formula (I).

In this further process of the invention 'N-alkylation' comprises the substitution of the N-atom depicted in formula (X) by any group R_5/R_6 as hereinbefore defined. This may be achieved by reaction of the

compound of formula (X) with a compound R_5Q_4 or R_6Q_4 wherein R_5 and R_6 are as hereinbefore defined and Q_4 is a leaving group.

Suitable values for Q_4 include groups displaced by nucleophiles such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$.

Favoured values for Q_4 include Cl, Br and I.

The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slight above.

Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions when the group R_5 or R_6 in the compound of formula (I) contains a methylene group adjacent to the N-atom in the bicycle.

Interconverting R_5 or R_6 in the compound of the formula (X) before coupling with the compound of the formula (V) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R_5/R_6 interconversion.

When R_5 or R_6 in the compound of formula (VI) contains a methylene group adjacent to the N-atom in the bicycle it is often convenient in the preparation of such a compound of formula (VI) to prepare the corresponding compound wherein the methylene group is replaced by

-CO-, or for R_5 or R_6 is methyl, where the methyl group is replaced by esterified carboxyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (V).

The compounds of formula (V) and (VI) are known or are preparable analogously to, or routinely from, known compounds. Intermediates of formula (V) wherein G is H and X and Y are hydrogen may be prepared from the corresponding intermediate wherein X and Y are a bond. Intermediates of formula (V) wherein G is COQ_1 form an aspect of the invention.

Compounds of the formula (VI) wherein Z is of formula (c) may be prepared as described in European Patent Publication No. 115933 or by analogous methods thereto.

Compounds of the formula (X) are novel and form an aspect of the invention.

It will be realised that in the compound of the formula (I) the -CO-L-linkage may have an endo or exo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo and exo isomer may if desired be synthesised from the corresponding endo or exo form of the compound of the formula (VI).

Compounds of the formula (I) wherein X and Y are both hydrogen may be converted to the corresponding compounds wherein X and Y are a bond by conventional

oxidation, and this is the preferred method of preparation when X and Y are a bond. Compounds of the formula (I) wherein X and Y are a bond may be converted to the corresponding compounds wherein X and Y are hydrogen by reduction; however it is preferred that this is carried out on the compound of formula (V) wherein G is H prior to coupling.

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally. The acid addition salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT antagonists and it is thus believed may generally be used in the treatment or prophylaxis of migraine, cluster headaches and trigeminal neuralgia. Compounds which are 5-HT antagonists may also be of potential use in the treatment of CNS disorders such as anxiety and psychosis; arrhythmia, obesity and irritable bowel syndrome.

The compounds of the present invention also have anti-emetic activity; in particular that of preventing cytotoxic agent or radiation induced nausea and vomiting. Examples of cytotoxic agents include cisplatin, doxorubicin and cyclophosphamide.

The compounds of the present invention also have gastric motility enhancing activity, useful in the treatment of disorders such as retarded gastric emptying, dyspepsia, flatulence, oesophagal reflux and peptic ulcer.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable

vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions

are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of migraine, cluster headache, trigeminal neuralgia and/or emesis in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders herein-before described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.1 to 50 mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

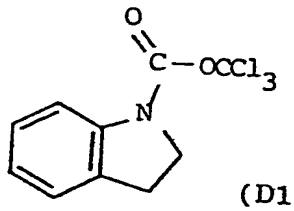
The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions illustrate the preparation of intermediates.

N.B. Nomenclature is based on Chemical Abstracts Index Guide 1977 published by the American Chemical Society.

Description 1

1-(2,3-Dihydro)-indolyltrichloromethyl carbamate (D1)



(D1)

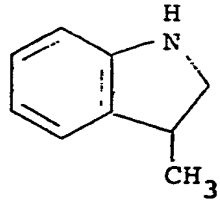
To 2,3-dihydroindole (5g) in dry dichloromethane (140ml) and triethylamine (5.85ml) at 0° was added dropwise trichloromethyl chloroformate (5ml) in dry dichloromethane (20ml). The reaction mixture was stirred at room temperature for 2h, then washed with water (5ml) and 5N hydrochloric acid solution (5ml). The organic phase was dried (Na_2SO_4), the solvent evaporated in vacuo and the residue purified by filtration through a short alumina column, eluting with dichloromethane to give the title compound (D1) (8.5g, 72%) as a buff solid m.p. 59-60°.

^{1}H-NMR ($CDCl_3$) 60MHz

δ	7.85-7.55	(m, 1H)
	7.30-6.70	(m, 3H)
	4.25-3.70	(m, 2H)
	3.25-2.80	(m, 2H)

Description 2

2,3-Dihydro-3-methylindole (D2)



(D2)

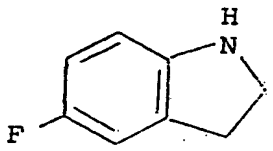
Following the procedure outlined by G.W. Gribble and J.H. Hoffman, Synthesis 859, 1977, 3-methyl indole (5g) was converted to the title compound (D2) (4.17g, 82%).

^{1}H NMR ($CDCl_3$) 60MHz

δ 7.30-6.30 (m, 4H)
3.80-2.80 (m, 4H)
1.30 (d, 3H)

Description 3

2,3-Dihydro-5-fluoroindole (D3)



(D3)

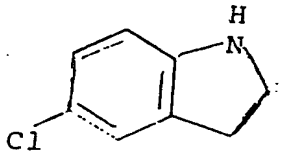
Following the procedure outlined in Description 2, 5-fluoroindole (3g) was converted to the title compound (D3) (2.54g, 84%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ 7.05-6.10 (m, 3H)
4.10-2.60 (m, 5H)

Description 4

2,3-Dihydro-5-chloroindole (D4)



(D4)

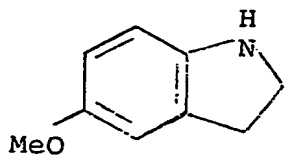
Following the procedure outlined in Description 2, 5-chloroindole (0.86g) was converted to the title compound (D4) (0.84g, 97%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ	7.30-6.65	(m, 2H)
	6.60-6.25	(m, 1H)
	4.10-3.25	(m, 3H)
	3.20-2.70	(m, 2H)

Description 5

2,3-Dihydro-5-methoxyindole (D5)



(D5)

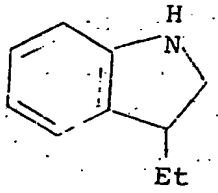
A solution of 5-methoxyindole (1g) in glacial acetic acid (20ml) was hydrogenated over platinum oxide (0.27g) at room temperature. After absorption of the theoretical amount of hydrogen (153ml), the catalyst was filtered off and the solvent evaporated in vacuo. The residue was basified with saturated potassium carbonate solution and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), the solvent evaporated in vacuo to give the title compound (D5) (0.43g, 42%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ	6.85-6.35	(m, 3H)
	3.65	(s, 3H)
	3.60-2.70	(m, 5H)

Description 6

2,3-Dihydro-3-ethylindole (D6)



(D6)

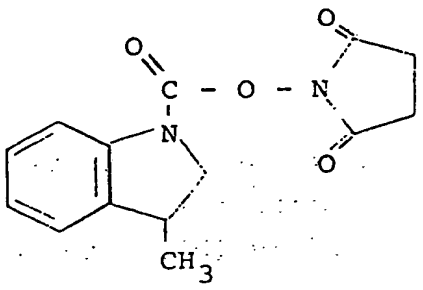
Following the procedure outlined in Description 2, 3-ethylindole (2.3g) (J.T. Fitzpatrick and R.D. Hiser, J. Org. Chem., 22, 1703-4, 1957) was converted to the title compound (D6) (1.3g, 56%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ	7.20-6.40	(m, 4H)
	3.90-2.90	(m, 4H)
	2.10-0.8	(m, 2H)
	0.9	(t, 3H)

Description 7

1-(2,3-Dihydro-3-methyl)indolyl-O-(1-succinimidyl)-carbamate (D7)



(D7)

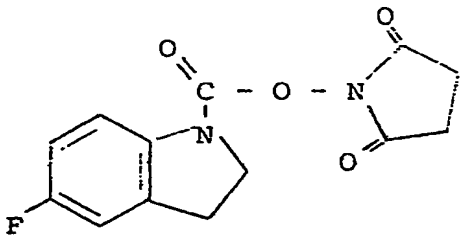
N,N-Disuccinimidyl carbonate (8.03g) and 2,3-dihydro-3-methylindole (D2) (4.17g) in dry toluene (150ml) was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue dissolved in dichloromethane, washed with 5N hydrochloric acid solution (10ml), saturated potassium bicarbonate (10ml) and brine (30ml). The organic phase was dried (Na_2SO_4), evaporated in vacuo and the residue purified by filtration through a short silica column, eluting with dichloromethane to give the title compound (D7) (6.85g, 80%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ	7.85-6.80	(m, 4H)
	4.60-4.00	(m, 1H)
	3.95-3.10	(m, 2H)
	2.75	(s, 4H)
	1.30	(bd, 3H)

Description 8

1-(2,3-Dihydro-5-fluoro)indolyl-O-(1-succinimidyl)-carbamate (D8)



(D8)

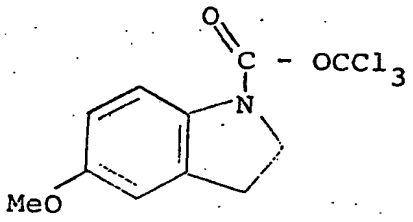
Following the procedure outlined in Description 7, reaction of N,N-disuccinimidyl carbonate (4.75g) with 2,3-dihydro-5-fluoroindole (D3) afforded the title compound (D8) (5g, 97%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ	7.90-7.60	(m, 1H)
	7.30-6.60	(m, 3H)
	4.40-4.00	(m, 2H)
	3.40-2.90	(m, 2H)
	2.85	(s, 4H)

Description 9

1-(2,3-Dihydro-5-methoxy)indolyl trichloromethyl carbamate (D9)



(D9)

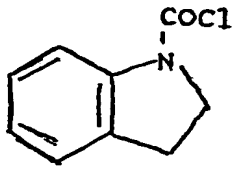
Following the procedure outlined in Description 1, reaction of 2,3-dihydro-5-methoxyindole (D5) (0.43g) with trichloromethylchloroformate (0.35ml) afforded the title compound (D9) (0.52g, 58%).

^{1}H-NMR ($CDCl_3$) 60MHz

δ	7.88-7.58	(m, 1H)
	6.85-6.48	(m, 2H)
	4.35-3.80	(m, 2H)
	3.70	(s, 3H)
	3.35-2.80	(m, 2H)

Description 10

1-(2,3-Dihydro)indolylcarbonyl chloride (D10)

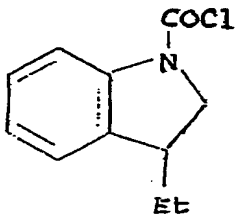


(D10)

To phosgene [110ml (12.5% w/w solution in toluene)] in dry dichloromethane (150ml) at 0° was added dropwise a solution of triethylamine (17ml) and freshly distilled 2,3-dihydroindole (14.5g) in dry dichloromethane (100ml). The reaction mixture was then stirred at 0° for 1h, and then poured into pentane (2.5l), washed with 5N sulphuric acid solution (100ml) and brine (100ml). The organic phase was dried (Na_2SO_4), the solvent evaporated in vacuo and the residue triturated with 60/80 pet. ether to give the title compound (D10) (18.37g, 83%).

Description 11

1-(2,3-Dihydro-3-ethyl)indolylcarbonyl chloride (D11)

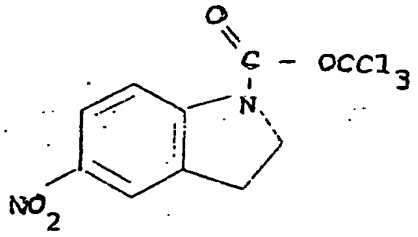


(D11)

Following the procedure outlined in Description 10, reaction of 2,3-dihydro-3-ethylindole (D6) (1.25g) with phosgene [7.7ml (12.5% w/w solution in toluene)] ... afforded the title compound (D11) (1.6g, 90%).

Description 12

1-(2,3-Dihydro-5-nitro)indolyl-trichloromethyl carbamate (D12)



(D12)

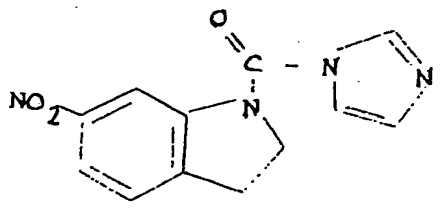
Following the procedure outlined in Description 1, reaction of 2,3-dihydro-5-nitroindole (4.72g) with trichloromethylchloroformate (3.44ml) afforded the title compound (D12) (5.5g, 59%)

^{1}H-NMR ($CDCl_3$) 60MHz

δ 8.80-7.10 (m, 3H)
4.70-3.90 (m, 2H)
3.50-2.95 (m, 2H)

Description 13

1-[1-(2,3-Dihydro-6-nitro)indolylcarbonyl]imidazole (D13)

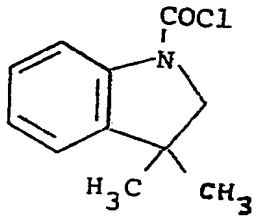


(D13)

2,3-Dihydro-6-nitroindole (3g) and 1,1'-carbonyldiimidazole (2.96g) in dry toluene (75ml) was heated under reflux for 5h. The reaction mixture was cooled and the solvent evaporated in vacuo. The residue was dissolved in dichloromethane (100ml) and washed with 5N hydrochloric acid solution (10ml) and water (20ml). The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo to give the title compound (D13) (4.7g, 100%).

Description 14

1-(2,3-Dihydro-3,3-dimethyl)indolylcarbonyl chloride (D14)

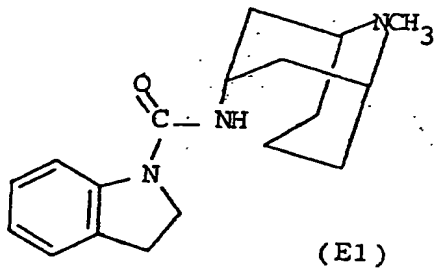


(D14)

Following the procedure outlined in Description 10, reaction of 2,3-dihydro-3,3-dimethylindole (2.7g) with phosgene [16.5ml (12.5% w/w solution in toluene)] afforded the title compound (D14) (3.5g, 91%).

Example 1

endo-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-2,3-dihydroindole-1-carboxamide (E1)



(E1)

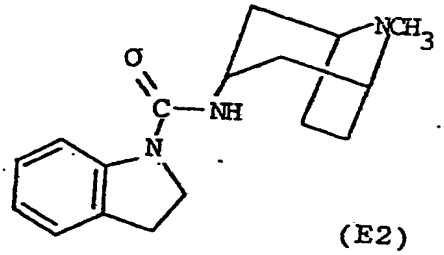
To 1-(2,3-dihydro)-indolyltrichloromethyl carbamate (D1) (3.64g) in dry toluene (100ml) was added endo-3-amino-9-methyl-9-azabicyclo[3.3.1]nonane (2g) in dry toluene (20ml). The reaction mixture was heated under reflux for 24h, then the solvent evaporated in vacuo. The residue was extracted with dichloromethane (200ml) and washed with saturated potassium carbonate solution (2 x 20ml). The organic phase was dried (Na_2SO_4) concentrated and the residue purified by column chromatography on alumina, eluting with $CHCl_3$ to give, after crystallisation from ethyl acetate, the title compound (E1) (2g, 52%) m.p. 176-8°.

^{1}H-NMR ($CDCl_3$) 270MHz

δ	7.85	(d, 1H)
	7.25-7.05	(m, 2H)
	6.95-6.85	(m, 1H)
	4.45-4.25	(m, 2H)
	4.00-3.80	(t, 2H)
	3.25-3.05	(m, 4H)
	2.65-2.40	(m, 2H)
	2.50	(s, 3H)
	2.15-1.85	(m, 3H)
	1.65-1.00	(m, 5H)

Example 2

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydroindole-1-carboxamide (E2)



(E2)

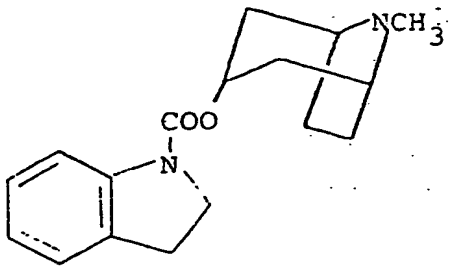
Following the procedure outlined in Example 1, reaction of 1-(2,3-dihydro)-indolyltrichloromethyl carbamate (D1) (0.64g) with endo-3-amino-8-methyl-8-azabicyclo-[3.2.1]octane (0.32g) afforded the title compound (E2) m.p. 153-4°

^{1}H-NMR ($CDCl_3$) 270MHz.

δ	7.85	(d, 1H)
	7.25-7.10	(m, 2H)
	6.95-6.85	(m, 1H)
	4.95	(bd, 1H)
	4.10	(q, 1H)
	3.90	(t, 2H)
	3.25-3.10	(m, 4H)
	2.25-2.05	(m, 4H)
	2.30	(s, 3H)
	1.90-1.75	(m, 4H)

Example 3

endo(8-Methyl-8-azabicyclo[3,2,1]oct-3-yl)-2,3-dihydroindole carboxylic acid ester (E3)



(E3)

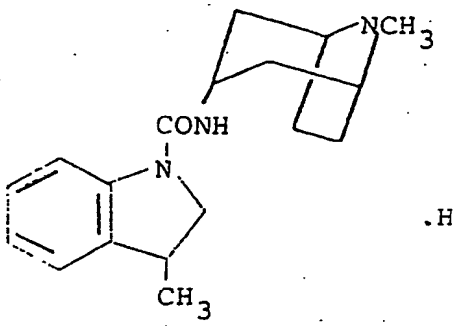
To 3-tropanol (1.13g) in diglyme (50ml) was added portionwise potassium t-butoxide (0.94g). The reaction mixture was stirred under an atmosphere of N_2 at room temperature for 1h and then the solvent was evaporated in vacuo. The resultant gum was redissolved in diglyme (50ml) and 1-(2,3-dihydro)indole trichloromethyl carbamate (D1) (1.5g) was added. The reaction mixture was heated under reflux for 36h, then cooled and evaporated in vacuo. The residue was dissolved in 5N hydrochloric acid solution (10ml) and washed with diethyl ether (30ml). The aqueous phase was basified with potassium carbonate and extracted with dichloromethane (3 x 75ml). The organic phase was dried (Na_2SO_4), the solvent evaporated in vacuo and the residue purified by column chromatography on alumina eluting with dichloromethane to give, after crystallisation from diethyl ether the title compound (E3) (0.5g, 31%). m.p. 133-4°.

^{1}H-NMR ($CDCl_3$) 270MHz

δ	7.85	(bd, 1H)
	7.22-7.12	(m, 2H)
	7.00-6.92	(m, 1H)
	5.05	(t, 1H)
	4.06	(t, 2H)
	3.28-3.08	(m, 4H)
	2.32	(s, 3H)
	2.32-1.75	(m, 8H)

Example 4

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-methylindole-1-carboxamide hydrochloride (E4)



.HCl

(E4)

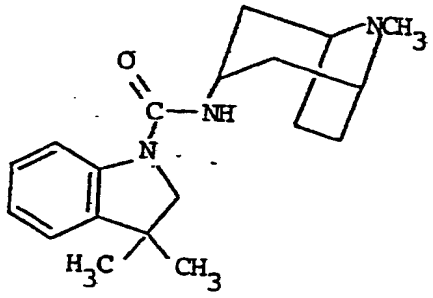
Triethylamine (1.8ml), 1-(2,3-dihydro-3-methyl)indolyl-O-(1-succinimidyl)carbamate (D7) (3.5g) and endo-3-amino-8-azabicyclo[3,2,1]octane (1.8g) were dissolved in dry toluene (100ml) and heated under reflux overnight. The reaction mixture was cooled and the solvent evaporated in vacuo. The residue was extracted with dichloromethane (200ml) and washed with saturated potassium carbonate solution (2 x 20ml). The organic phase was dried (Na_2SO_4), concentrated and the residue purified by column chromatography on alumina, eluting with chloroform. The product was isolated as the hydrochloride salt (E4) (0.97g, 23%). m.p. 268-70°.

^{1}H-NMR (d_6-DMSO) 270MHz

10.35-10.05	(m,	1H)
7.75	(d,	1H)
7.25-7.05	(m,	2H)
6.95-6.85	(m,	1H)
6.29	(bs,	1H)
4.15	(t,	1H)
3.90-3.70	(m,	3H)
3.65-3.30	(m,	2H)
2.65	(s,	3H)
2.50-2.10	(m,	8H)
1.26	(d,	3H)

Example 5

endo-N-(8-Methyl-8-azabiyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole-1-carboxamide (E5):



(E5)

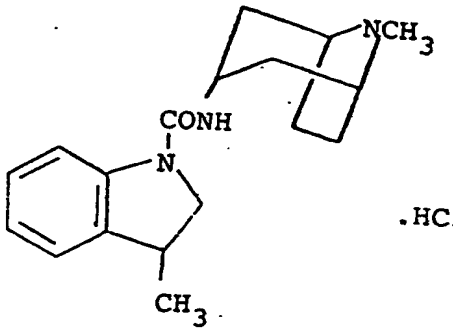
Following the procedure outlined in Example 14, reaction of 1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride (D14) (1.2g) with endo-3-amino-8-azabicyclo-[3.2.1]octane (0.8g) afforded the title compound (E5) (0.88g, 50%) m.p. 158-9°.

^{1}H-NMR $CDCl_3$

7.80	(d, 1H)
7.25-7.05	(m, 2H)
7.00-6.90	(m, 1H)
6.92	(bd, 1H)
4.08	(q, 1H)
3.60	(s, 2H)
3.30-3.15	(m, 2H)
2.35	(s, 3H)
2.40-2.10	(m, 4H)
1.95-1.65	(m, 4H)
1.35	(s, 6H)

Example 6

endo-N-(8-Methyl-8-azabicyclo[3,2,1]oct-3-yl)-3-methyl-indole-1-carboxamide hydrochloride (E6)



.HCl

(E6)

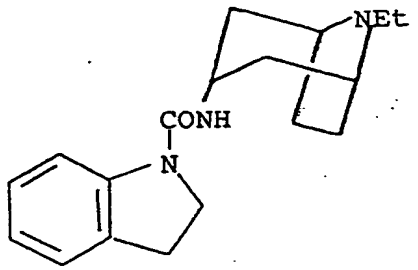
endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-methylindole-1-carboxamide hydrochloride (E4) (0.5g) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.41g) in dry chloroform (100ml) were heated under reflux for 6h. The reaction mixture was cooled and washed with saturated potassium carbonate solution (20ml). The organic phase was dried (Na_2SO_4), concentrated and the residue filtered through a short alumina column, eluting with chloroform. The product was isolated as the hydrochloride salt (E6) (0.2g, 40%). m.p. 158-61°

^1H-NMR (d_6-DMSO) 400MHz

δ	10.50	(bs, 1H)
	8.15	(d, 1H)
	7.85	(bs, 1H)
	7.65	(s, 1H)
	7.55	(d, 1H)
	7.30-7.15	(m, 2H)
	4.00-3.75	(m, 3H)
	2.65	(bs, 3H)
	2.50-2.05	(m, 11H)

Example 7

endo-N-(8-Ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydroindole-1-carboxamide (E7)



(E7)

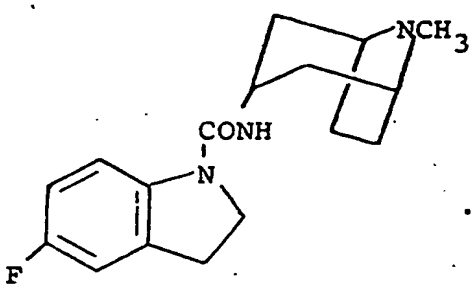
Following the procedure outlined in Example 1, reaction of 1-(2,3-dihydro)indole-trichloromethyl carbamate (D1) (0.91g) with endo-3-amino-8-ethyl-8-azabicyclo-[3.2.1]octane (0.5g) afforded the title compound (E7) (0.24g, 25%) m.p. 140-1°.

^{1}H-NMR ($CDCl_3$) 270MHz

δ		
	7.85	(d, 1H)
7.25-7.10		(m, 2H)
6.95-6.85		(m, 1H)
	4.95	(bd, 1H)
	4.10	(q, 1H)
	3.90	(t, 2H)
	3.35	(bs, 2H)
	3.15	(t, 2H)
	2.45	(q, 2H)
2.38-2.20		(m, 2H)
2.18-2.00		(m, 2H)
1.95-1.65		(m, 4H)
	1.10	(t, 3H)

Example 8

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-5-fluoro-2,3-dihydroindole-1-carboxamide hydrochloride (E8)



.HCl

(E8)

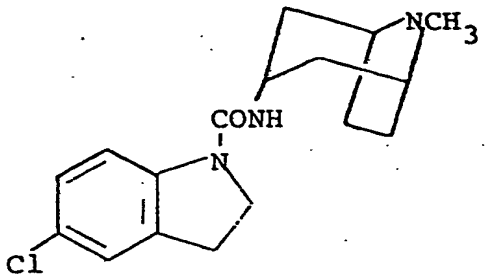
Following the procedure outlined in Example 4, reaction of 1-(2,3-dihydro-5-fluoro)indolyl-O-(1-succinimidyl)-carbamate (D8) (3.5g) with triethylamine (1.75ml) and endo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane (1.76g) afforded the free base, which was converted to the hydrochloride salt (E8) (1.11g, 18%) m.p. 299-300° (decomposition).

^{1}H-NMR (d_6-DMSO) 270MHz

δ	10.35-10.15	(m, 1H)
	7.80-7.70	(m, 1H)
	7.10-6.85	(m, 2H)
	6.30	(bs, 1H)
	4.05	(t, 2H)
	3.90-3.70	(m, 3H)
	3.10	(t, 2H)
	2.65	(bs, 3H)
	2.50-2.05	(m, 8H)

Example 9

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-5-chloroindole-1-carboxamide (E9)



(E9)

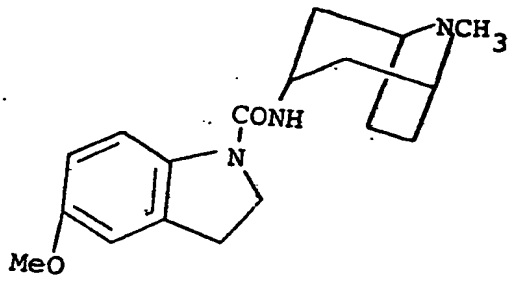
To phosgene [3.8ml (12.5% w/w solution in toluene)] in dry dichloromethane (50ml) was added dropwise 2,3-dihydro-5-chloroindole (D4) (0.83g) in CH_2Cl_2 (20ml). Triethylamine (0.83ml) was then added and the whole stirred at room temperature for 10 min. endo-3-Amino-8-methyl-8-azabicyclo[3.2.1]octane (0.83g) in dry dichloromethane (10ml) was added and the reaction mixture stirred at room temperature for 2h, then washed with saturated potassium bicarbonate solution (15ml) and brine (20ml). The organic phase was dried (Na_2SO_4), the solvent evaporated in vacuo and the residue column chromatographed on alumina eluting with chloroform to give, after crystallisation from ethyl acetate, the title compound (E9) (0.36g, 19%) m.p. 149-50°.

^{1}H-NMR ($CDCl_3$) 400MHz

δ	7.81 (d, 1H)
	7.15-7.05 (m, 2H)
	4.90 (bd, 1H)
	4.08 (q, 1H)
	3.91 (t, 2H)
	3.28-3.10 (m, 4H)
	2.34 (s, 3H)
	2.35-2.08 (m, 4H)
	1.90-1.65 (m, 4H)

Example 10

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)2,3-dihydro-5-methoxyindole-1-carboxamide (E10)



(E10)

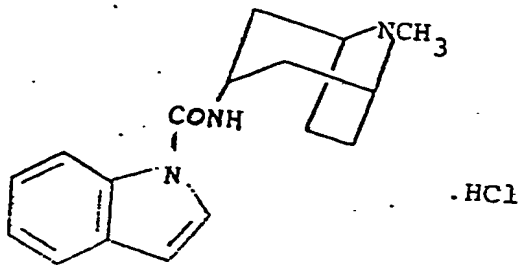
Following the procedure outlined in Example 1, reaction of 1-(2,3-dihydro-5-methoxy)indolyl trichloromethyl carbamate (D9) (0.48g) with endo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane (0.23g) afforded the title compound (E10) (0.22g, 45%) m.p. 142-5°.

^{1}H-NMR ($CDCl_3$) 270MHz

δ	7.75	(d, 1H)
	6.80-6.65	(m, 2H)
	4.88	(bd, 1H)
	4.08	(q, 1H)
	3.90	(t, 2H)
	3.78	(s, 3H)
	3.28-3.10	(m, 4H)
	2.32	(s, 3H)
	2.40-2.10	(m, 4H)
	1.90-1.65	(m, 4H)

Example 11

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)indole-1-carboxamide hydrochloride (E11)



(E11)

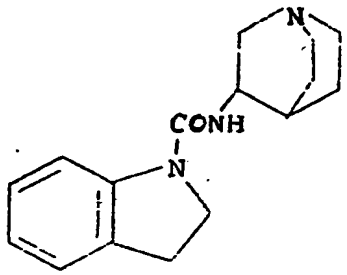
Following the procedure outlined in Example 6, reaction of endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)2,3-dihydroindole-1-carboxamide hydrochloride (E2) (0.46g) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.44g) afforded the title compound (E11) (0.31g, 68%) m.p. 258-60° (decomposition).

^{1}H-NMR (d_6-DMSO) 270MHz

δ	10.6-10.3	(m, 1H)
	8.15-7.95	(m, 2H)
	7.85	(d, 1H)
	7.65-7.55	(m, 1H)
	7.35-7.10	(m, 2H)
	6.75-6.65	(m, 1H)
	4.05-3.65	(m, 3H)
	2.65	(bs, 3H)
	2.60-2.00	(m, 8H)

Example 12

N-(1-Azabicyclo[2.2.2]oct-3-yl)2,3-dihydroindole-1-carboxamide hydrochloride (E12)



(E12)

A mixture of 3-amino-1-azabicyclo[2.2.2]octane (0.5g) and triethylamine (0.7ml) in dry dimethylformamide (30ml) was heated at 50° for 1h. The solution was cooled and added dropwise to a solution of 1-(2,3-dihydro)indolylcarbonyl chloride (D10) (0.46g) and triethylamine (0.35ml) in dry dimethylformamide (50ml) at 0°. The reaction mixture was stirred at room temperature for 2h, the solvent was then evaporated in vacuo. The residue was dissolved in dichloromethane and washed with 10% sodium hydroxide solution (10ml). The organic phase was dried (Na_2SO_4), the solvent evaporated in vacuo and the residue was column chromatographed on alumina, eluting with chloroform. The product was isolated as the hydrochloride salt (E12) (0.16g, 21%) m.p. 138-40°.

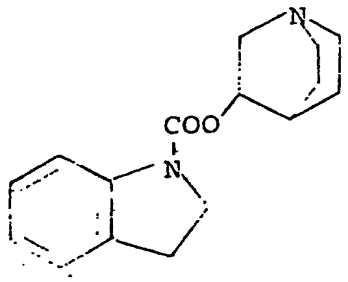
^{1}H-NMR (d_6-DMSO) 400MHz

δ	10.7-10.3	(m, 1H)
	7.82	(d, 1H)
	7.16	(d, 1H)
	7.08	(t, 1H)
	6.86	(t, 1H)
	6.80	(d, 1H)

4.18-4.08 (m, 1H)
4.06-3.92 (m, 2H)
2.54 (t, 1H)
2.46-3.04 (m, 7H)
2.18-2.06 (m, 2H)
1.96-1.78 (m, 2H)
1.76-1.60 (m, 1H)

Example 13

N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,3-dihydroindole-1-carboxylic acid ester (E13)



(E13)

To 1-azabicyclo[2.2.2]octan-3-ol (1g) in dry tetrahydrofuran (75ml) at -78° under an atmosphere of nitrogen, was added dropwise n-butyl lithium [5.2ml (1.6M solution in hexanes)]. The mixture was allowed to warm to room temperature and then stirred for 10 min. The reaction mixture was cooled to -78° and 2,3-dihydroindole (1.43g) in dry tetrahydrofuran (20ml) was added dropwise. The reaction mixture was again allowed to warm to room temperature and stirred overnight. Water was added and the whole evaporated *in vacuo*, the residue was dissolved in dichloromethane (150ml) and washed with saturated potassium carbonate solution (30ml). The organic phase was dried (Na_2SO_4), the solvent was evaporated *in vacuo* and the residue column chromatographed on alumina, eluting with chloroform to give, after crystallisation from ethyl acetate, the title compound (E13) (0.29g, 14%) m.p. 124-5°.

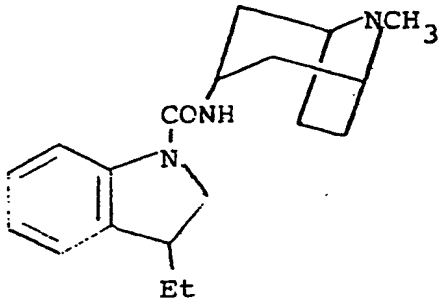
^{1}H-NMR ($CDCl_3$) 270MHz

δ	8.00-7.70	(m, 1H)
	7.30-7.10	(m, 2H)
	7.05-6.90	(m, 1H)
	5.05-4.80	(m, 1H)

4.20-3.95 (m, 2H)
3.45-3.25 (m, 1H)
3.25-2.50 (m, 7H)
2.30-2.05 (m, 1H)
2.05-1.20 (m, 4H)

Example 14

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethylindole-1-carboxamide hydrochloride (E14)



(E14)

To 1-(2,3-dihydro-3-ethyl)indolylcarbonyl chloride (D11) (1g) in dry dichloromethane (100ml) was added dropwise a mixture of endo-3-amino-8-azabicyclo[3,2,1] octane (0.7g) and triethylamine (0.7ml) in dry dichloromethane (50ml). The reaction mixture was stirred at room temperature overnight, the solvent was then evaporated in vacuo. The residue dissolved in 5N hydrochloric acid solution (20ml) and washed with diethyl ether (50ml). The aqueous phase was basified with potassium carbonate and then extracted with dichloromethane (3 x 75ml). The organic phase was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue filtered through a short alumina column. The product was isolated as the hydrochloride salt (E14) (1.27g, 76%) m.p. 263-4°.

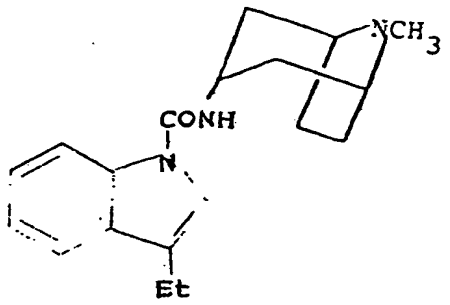
^1H-NMR (d_6-DMSO) 270MHz

δ	10.80-10.20	(m, 1H)
	7.80	(d, 1H)
	7.25-7.05	(m, 2H)
	6.95-6.80	(m, 1H)
	6.32	(bs, 1H)
	4.10	(t, 1H)
	3.90-3.65	(m, 4H)
	3.55-3.10	(m, 1H)

2.65	(bs, 3H)
2.60-2.00	(m, 8H)
1.90-1.65	(m, 1H)
1.60-1.40	(m, 1H)
0.92	(t, 3H)

Example 15

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-ethyl-indole-1-carboxamide hydrochloride (E15)



.HCl

(E15)

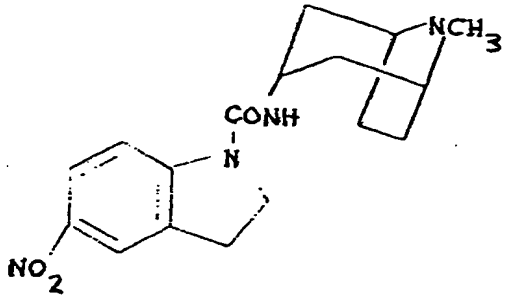
Following the procedure outlined in Example 6, reaction of endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)2,3-dihydro-3-ethylindole-1-carboxamide hydrochloride (E14) (1.01g) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.8g) afforded the title compound (E15) (0.4g, 40%) m.p. 210-13°.

^{1}H-NMR (d_6-DMSO) 270MHz

δ	10.90-10.50	(m, 1H)
	8.15	(d, 1H)
	7.90	(bs, 1H)
	7.68	(s, 1H)
	7.55	(d, 1H)
	7.35-7.10	(m, 2H)
	4.10-3.65	(m, 3H)
	2.90-2.05	(m, 13H)
	1.30	(t, 3H)

Example 16

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-5-nitroindole-1-carboxamide (E16)



(E16)

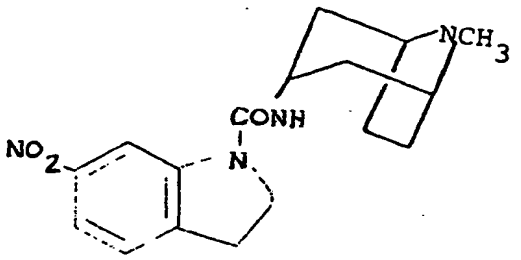
Following the procedure outlined in Example 1, reaction of 1-(2,3-dihydro-5-nitro)indolyl trichloromethyl carbamate (D12) (2g) with endo-3-amino-8-azabicyclo-[3.2.1]octane (0.9g) afforded the title compound (E16) (1.25g, 62%) m.p. 176-8°.

^{1}H-NMR ($CDCl_3$) 270MHz

δ	8.18-7.95	(m, 3H)
	5.05	(bd, 1H)
	4.15-3.95	(m, 3H)
	3.35-3.15	(m, 4H)
	2.30	(s, 3H)
	2.35-2.10	(m, 4H)
	1.85-1.60	(m, 4H)

Example 17

endo-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-6-nitroindole-1-carboxamide hydrochloride (E17)



.HCl

(E17)

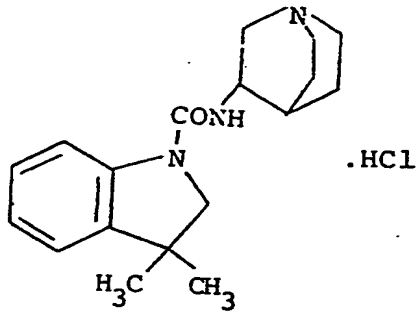
Following the procedure outlined in Example 1, reaction of 1-[1-(2,3-dihydro-6-nitro)indolylcarbonyl]imidazole (D13) (4.7g) with endo-3-amino-8-methyl-8-azabicyclo[3.2.1]octane (2.55g) afforded the title compound (E17) m.p. 245-7° (decomposition).

^{1}H-NMR (d_6-DMSO) 270MHz)

δ	10.15-9.95	(m, 1H)
	8.55	(d, 1H)
	7.85-7.70	(m, 1H)
	7.45-7.35	(m, 1H)
	6.65-6.55	(m, 1H)
	4.15	(t, 2H)
	3.90-3.70	(m, 1H)
	3.60-3.35	(m, 2H)
	3.30-3.15	(t, 2H)
	2.65	(d, 3H)
	2.45-2.00	(m, 8H)

Example 18

N-(1-Azabicyclo[2.2.2]oct-3-yl)2,3-dihydro-3,3-dimethyl indole-1-carboxamide hydrochloride (E18)



.HCl

(E18)

To a solution of 3-amino-1-azabicyclo[2.2.2]octane dihydrochloride (0.87g) in water (1.5ml) was added dry dimethylformamide (30ml) and triethylamine (2ml). The mixture was stirred at room temperature for 5 min, then a solution of 1-(2,3-dihydro-3,3-dimethyl)indolyl-carbonyl chloride (D14) in dry dimethylformamide (20ml) was added dropwise. The reaction mixture was stirred at room temperature for 18h, the solvent was then evaporated in vacuo. The residue was dissolved in 5N hydrochloric acid solution (25ml) and washed with diethyl ether (50ml). The aqueous phase was basified with potassium carbonate and then extracted with dichloromethane (3 x 75ml). The organic phase was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue crystallised from ethyl acetate/diethyl ether to give the title compound (E18) m.p. 174-6°.

^{1}H-NMR ($CDCl_3$) 270MHz

11.40	(bs, 1H)
7.95	(d, 1H)
7.25-7.05	(m, 2H)
6.95	(t, 1H)
6.65	(bd, 1H)
4.60-4.40	(m, 1H)

4.28 (dd, 1H)
4.10-3.80 (m, 3H)
3.55-3.35 (m, 1H)
3.30-3.00 (m, 3H)
2.50-2.30 (m, 2H)
2.25-1.90 (m, 1H)
1.95-1.60 (m, 2H)
1.35 (s, 6H)

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

The compounds were evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats, 250-350g, were anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) was given repeatedly by the intravenous route and changes in heart rate quantified. Compounds were given intravenously and the concentration required to reduce the 5HT-evoked response to 50% of the control response (ED_{50}) was then determined.

The results were as shown in Table 1.

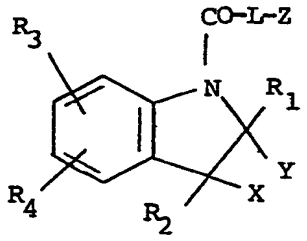
Table 1

Compound of Example No.	ED_{50} µg/kg i.v
1	12.5
2	1.4
3	5
4	3
5	0.58
6	1.6
7	>10
8	17
9	>10
10	7
11	7.7
12	4.4
13	3.9
14	1.0
15	2.0
16	>10
17	>10
18	5.3

C

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

L is NH or O;

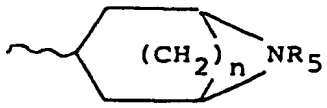
X and Y are independently selected from hydrogen or C_{1-4} alkyl, or together are a bond;

R_1 and R_2 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl-C_{1-4} alkyl, or together are C_{2-4} polymethylene;

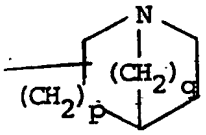
R_3 and R_4 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl,

phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5} polymethylene;

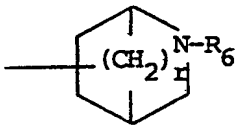
Z is a group of formula (a), (b) or (c)



(a)



(b)

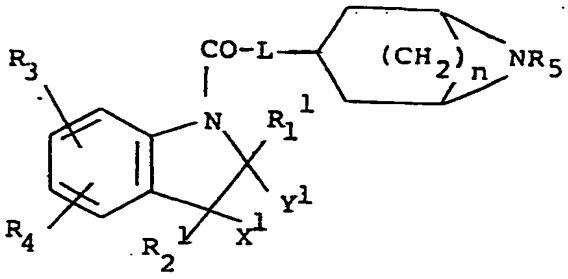


(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl.

2. A compound according to claim 1 of formula (II):



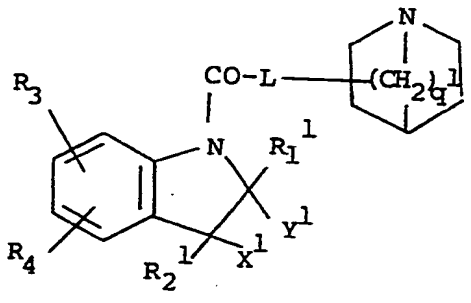
(II)

wherein X^1 and Y^1 are independently hydrogen, methyl or ethyl, or together are a bond, $R_1{}^1$ and $R_2{}^1$ are independently hydrogen, methyl or ethyl and the remaining variables are as defined in claim 1.

3. A compound according to claim 2 wherein n is 2.

4. A compound according to claim 2 or 3 wherein R_5 is methyl.

5. A compound according to claim 1 of formula (III):



(III)

wherein q^1 is 1 or 2 and the remaining variables are as defined in claims 1 and 2.

6. A compound according to claim 5 wherein q^1 is 2.

7. A compound according to any one of claims 1 to 6 wherein one of R_3 and R_4 is hydrogen and the other is selected from hydrogen, 5-chloro and 5-fluoro.

8. A compound according to any one of claims 1 to 7 wherein L is NH.

9. endo-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl) -2,3-dihydroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl) -2,3-dihydroindole-1-carboxamide,

endo(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-2,3-dihydroindole carboxylic acid ester,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl) -2,3-dihydro-3-methylindole-1-carboxamide,

endo-N-(8-methyl-8-azabiyclo[3.2.1]oct-3-yl) -2,3-dihydro-3,3-dimethylindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl) -3-methyl-indole-1-carboxamide,

endo-N-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl) -2,3-dihydroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl) -5-fluoro-2,3-dihydroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-5-chloroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-5-methoxyindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-indole-1-carboxamide,

N-(1-azabicyclo[2.2.2]oct-3-yl)2,3-dihydroindole-1-carboxamide,

N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3-dihydroindole-1-carboxylic acid ester,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethylindole-1-carboxamide,

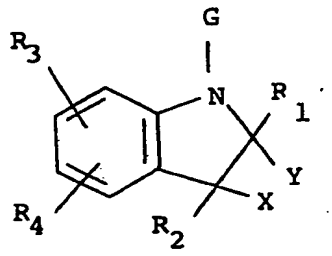
endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-ethylindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-5-nitroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-6-nitroindole-1-carboxamide,

N-(1-azabicyclo[2.2.2]oct-3-yl)2,3-dihydro-3,3-dimethylindole-1-carboxamide, or the hydrochloride salt of any of the foregoing.

10. A process for the preparation of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):



(V)

with a compound of formula (VI):

$$J\text{-}Z^1 \qquad \text{(VI)}$$

wherein

G is COQ_1 where Q_1 is a leaving group, or hydrogen; and, when G is COQ_1, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage with the compound of formula (V); Z^1 is Z as defined or wherein R_5/R_6 is replaced by a hydrogenolysable protecting group; and the remaining variables are as defined in claim 1; and thereafter optionally converting any R_3 and R_4 group to another R_3 and R_4 group respectively, converting Z^1, when other than Z, to Z; converting X and Y to other X and Y; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

11. A compound of formula (V) as defined in claim 10, wherein G is COQ_1.

12. 1-(2,3-Dihydro)-indolyltrichloromethyl carbamate,

1-(2,3-dihydro-3-methyl)indolyl-O-(1-succinimidyl)carbamate,

1-(2,3-dihydro-5-fluoro)indolyl-O-(1-succinimidyl)carbamate,

1-(2,3-dihydro-5-methoxy)indolyl trichloromethyl carbamate,

1-(2,3-dihydro)indolylcarbonyl chloride,

1-(2,3-dihydro-3-ethyl)indolylcarbonyl chloride,

1-(2,3-dihydro-5-nitro)indolyl-trichloromethyl carbamate,

1-[1-(2,3-dihydro-6-nitro)indolylcarbonyl]-imidazole, or

1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, and a pharmaceutically acceptable carrier.

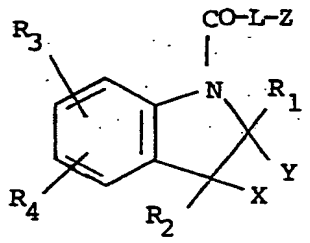
14. A compound according to any one of claims 1 to 9, for use as an active therapeutic substance.

15. A compound according to any one of claims 1 to 9 for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

16. Use of a compound according to any one of claims 1 to 9 in the preparation of a medicament for the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

Claims FOR SPAIN.

1. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

L is NH or O;

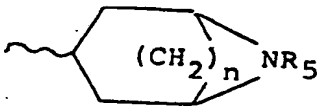
X and Y are independently selected from hydrogen or C_{1-4} alkyl, or together are a bond;

R_1 and R_2 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl-C_{1-4} alkyl, or together are C_{2-4} polymethylene;

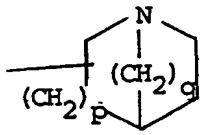
R_3 and R_4 are independently selected from hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulphonylamino, N-(C_{1-6} alkylsulphonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulphinyl, hydroxy, nitro or amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C_{1-4} alkylamino optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl,

phenyl or phenyl C_{1-4} alkyl groups or optionally N-disubstituted by C_{4-5} polymethylene;

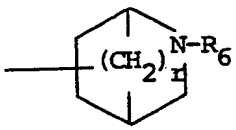
Z is a group of formula (a), (b) or (c)



(a)



(b)

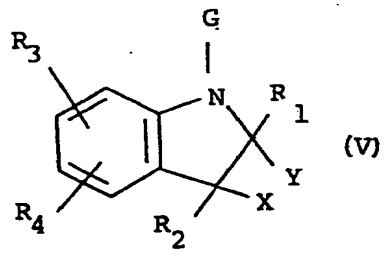


(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl or C_{2-7} alkenyl-C_{1-4} alkyl;

which process comprises reacting a compound of formula (V):



(V)

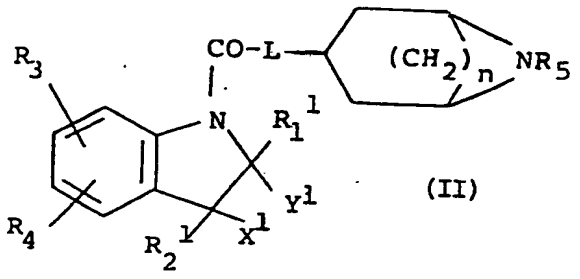
with a compound of formula (VI):

$$J\text{-}Z^1 \qquad \text{(VI)}$$

wherein

G is COQ_1 where Q_1 is a leaving group, or hydrogen; and, when G is COQ_1, J is NH_2, or OH or a reactive derivative thereof or, when G is hydrogen, J is a group containing an activated carbonyl group capable of forming a CO-L-linkage with the compound of formula (V); Z^1 is Z as defined or wherein R_5/R_6 is replaced by a hydrogenolysable protecting group; and the remaining variables are as defined in claim 1; and thereafter optionally converting any R_3 and R_4 group to another R_3 and R_4 group respectively, converting Z^1, when other than Z, to Z; converting X and Y to other X and Y; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

2. A process for the preparation of a compound according to claim 1 of formula (II):



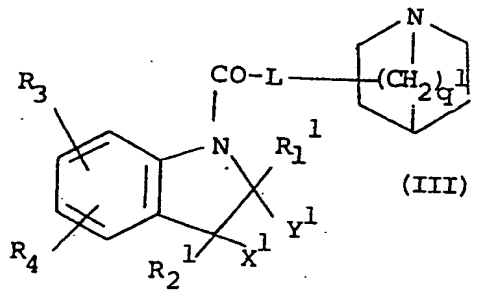
(II)

wherein X^1 and Y^1 are independently hydrogen, methyl or ethyl, or together are a bond, $R_1{}^1$ and $R_2{}^1$ are independently hydrogen, methyl or ethyl and the remaining variables are as defined in claim 1.

3. A process according to claim 2 wherein n is 2.

4. A process according to claim 2 or 3 wherein R_5 is methyl.

5. A process for the preparation of a compound according to claim 1 of formula (III):



(III)

wherein q^1 is 1 or 2 and the remaining variables are as defined in claims 1 and 2.

6. A process according to claim 5 wherein q^1 is 2.

7. A process according to any one of claims 1 to 6 wherein one of R_3 and R_4 is hydrogen and the other is selected from hydrogen, 5-chloro and 5-fluoro.

8. A process according to any one of claims 1 to 7 wherein L is NH.

9. A process according to claim 1 for the preparation of:

endo-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-2,3-dihydroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydroindole-1-carboxamide,

endo(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-2,3-dihydroindole carboxylic acid ester,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-methylindole-1-carboxamide,

endo-N-(8-methyl-8-azabiyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethylindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-3-methyl-indole-1-carboxamide,

endo-N-(8-ethyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)
-5-fluoro-2,3-dihydroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
2,3-dihydro-5-chloroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
2,3-dihydro-5-methoxyindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
indole-1-carboxamide,

N-(1-azabicyclo[2.2.2]oct-3-yl)2,3-
dihydroindole-1-carboxamide,

N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3-
dihydroindole-1-carboxylic acid ester,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
2,3-dihydro-3-ethylindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-
3-yl)-3-ethyl-indole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
2,3-dihydro-5-nitroindole-1-carboxamide,

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-
2,3-dihydro-6-nitroindole-1-carboxamide,

N-(1-azabicyclo[2.2.2]oct-3-yl)2,3-dihydro-
3,3-dimethylindole-1-carboxamide, or the hydrochloride
salt of any of the foregoing.

10. Use of a compound prepared by a process according to any one of claims 1 to 9 in the preparation of a medicament for the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

European Patent Office

EUROPEAN SEARCH REPORT

0247266

Application number

EP 86 31 0011

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	WO-A-85 01 048 (SANDOZ AG) * Claims 1-3,8,11,12,14,15 * ---	1,2,5,10,13-16	C 07 D 451/04 C 07 D 451/12 C 07 D 451/14 C 07 D 453/02 C 07 D 209/08 A 61 K 31/46 A 61 K 31/445
A	WO-A-84 00 166 (SANDOZ AG) * Claims 2-12 * & GB-A-2 125 398 (Cat. D) ---	1,2,5,10,13-16	
P,A	EP-A-0 200 444 (BEECHAM GROUP PLC) * Claims 1,2,4,12,13,15,16 * ---	1,2,5,10,13-16	
A,D	EP-A-0 158 265 (BEECHAM GROUP PLC) * Claims 1,2,5,10-13 * ---	1,2,10,13-16	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 D 209/00 C 07 D 403/00 C 07 D 451/00 C 07 D 453/00
A,D	GB-A-2 100 259 (M.TORAUDE & CIE) * Claims 1,16,22,24 * ---	1,2,10,13-16	
A,D	EP-A-0 115 933 (BEECHAM GROUP PLC) * Claims 2-4,8,10,12 * ---	1,10,13-16	

[redacted]

Place of search	Date of completion of the search	Examiner
Berlin	30-04-1987	HASS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503 03.82

European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

1) Claims 1-10,13-16: Compound of formula I, process for their preparation, and their use

2) Claims 11,12: Compounds of formula V seem not to contribute to the characteristics of the final products (cf: decision of the Technical Board of Appeal 3.3.1, no. T 65/82, dated April 20, 1983).

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.

namely claims:

☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims

namely claims: 1-10,13-16

Svensson, Leonard R.

From: San Diego RTA [sdrta@sdrta.org]
Sent: Wednesday, February 11, 2004 10:47 AM
To: lrs@bskb.com
Subject: Event Reminder: 4 RTA Winter 2004 Workshops Left - Limited Space.

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IP Litigation
For Executives

IP Litigation for Executives
Tuesday, February 17, 2004, 8:00 am-12:00pm

Essential Business IP and Regulatory Issues For Emerging
life sciences companies

Essential Business IP and Regulatory Issues for Emerging Life Sciences Companies
Wednesday, March 10, 2004, 8:00am-12:00pm



Preparing for and Negotiating the Sale of Your Private Company
Tuesday, March 16, 2004, 8:00am-12:00pm

the
VENTURE CAPITAL
process

The Venture Capital Process
Wednesday, March 24, 2004, 8:00am-12:00pm

IP Litigation
For Executives

IP Litigation for Executives
Tuesday, February 17, 2004, 8:00 am-12:00pm
Presented by

SHEPPARD MULLIN
SHEPPARD MULLIN RICHTER & HAMPTON LLP
ATTORNEYS AT LAW

Intellectual property (IP), in the form of copyrights, trademarks, trade secrets, and patents, is criti important in high-tech business. In today's economy, high tech companies can leverage their IP as to increase their valuation and add to their bottom line, whether through licensing or lawsuits.

Litigating IP disputes, however, can be a huge drain on a company's resources, both monetary and human. Careful planning can help companies avoid litigation on the one hand and enhance the rem available to companies who find that they must pursue litigation to protect their IP on the other ha Preparation includes using the proper legal employment documents, properly researching and regis your IP, and taking protective measures to secure your IP. Even when litigation appears to be unavoidable, there are many creative alternatives that should be considered before getting the cou involved.

This workshop presented by Sheppard Mullin will provide the audience with an overview of IP litiga issues from planning litigation avoidance, to planning litigation success, to considering alternatives litigation.

This activity has been approved for Minimum Continuing Legal Education credit by the State Bar of California in the amount of 3 hours. Sheppard, Mullin, Richter & Hampton LLP certifies that this act conforms to the standards for approved education activities prescribed by the rules and regulations the state bar of california governing minimum continuing legal education.

Topics to be covered include:

- Identifying your IP
- Understanding what can happen if you don't protect your IP
- Strategies for avoiding IP litigation
- Essential IP employment agreements
- IP litigation and digital technologies
- Case Examples

Click here for more info and to register.



Essential Business IP and Regulatory Issues for Emerging Life Sciences Companies
Presented By

FOLEY LARDNER
ATTORNEYS AT LAW

Wednesday, March 10, 2004, 8:00am-12:00pm

In order to succeed, an emerging life sciences company team must craft and implement a comprehensive business plan, protect its valuable intellectual property, and navigate through the complex regulatory waters posed by the FDA approval process. They must plan a strategy for assu that Medicare and other government programs will pay for its product. This workshop presented by & Lardner will provide valuable insights into each of these areas. Four experienced legal strategists specialize in corporate structure and capital formation, I.P. protection, FDA law and health care reimbursement will offer valuable insights.

Specific topics covered will include the following:

- Business Issues
o The need for a comprehensive business plan
o Obtaining capital; due diligence pitfalls
o Choice of legal entity
o Exit strategy

- Intellectual Property
o How to protect your product
o Crafting an I.P. strategy

- The FDA approval process for new devices and prescription drugs
o What you need to know when developing a new product

o The ins and outs of getting approval

- Health care reimbursement
o Overview of Medicare coverage for drugs and devices
o Securing coverage for a new product

When:
March 10th , 2004, 8:00am-12:00pm

Where:
Doubletree Hotel
11915 El Camino Real
San Diego, CA 92113

Cost: $45 pre-registered, $60 at the door

Click here for more info and to register.



Preparing for and Negotiating the Sale of Your Private Company
Tuesday, March 16, 2004, 8:00am-12:00pm
Presented by
MoFo
MORRISON & FOERSTER LLP
Lawyers for the global economy™

Your private company is far more likely to be acquired than to go public in an IPO, particularly und current market conditions. Therefore, it is critical that you understand early on the steps that you s take to prepare your company for an acquisition. It also is extremely valuable to have an understa of the key deal terms and contractual provisions on which you should focus. This Workshop presen Morrison & Foerster is geared towards entrepreneurs who want to know how to prepare for and successfully negotiate an acquisition of their companies.

Topics Covered Will Include:

- Avoiding early stage pitfalls that may impact an acquisition
- How to structure the acquisition
- Engaging investment bankers and other advisors
- How to use letters of intent and term sheets
- How to negotiate key deal terms and contractual provisions in acquisition agreements, and w they really matter

- What public company acquirers care about in the post-Sarbanes-Oxley world

Click here for more info and to register.

the VENTURE CAPITAL process

The Venture Capital Process
Wednesday, March 24, 2004, 8:00am-12:00pm
Presented by

Allen Matkins | Allen Matkins Leck Gamble & Mallory LLP *attorneys at law*

Raising Venture Capital: Expectations in today?s economy
Raising money in today's market is no easy task, but it can be done if you focus on the right things avoid common deal-killers.

The goal of this workshop presented by Allen Matkins is designed to provide you with information, expertise, and knowledge to prepare you for raising capital from venture capital funds.

What will the workshop cover?

- The Structure of Venture Funds
- The Venture Capital Process
- Fundamentals of Venture Capital Investment
- Key elements in structuring your company
- What investors look for in a company
- The signals that make a company attractive
- Valuation
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Svensson, Leonard R.

From: GORMAN, Susan W.
Sent: Wednesday, February 11, 2004 10:46 AM
To: Svensson, Leonard R.
Subject: MA_Parameters000 Table

Len,

Here are my notes on the parameters Table Sandra working on

1. Needs reformatting to make discrete columns
2. Needs column headings
 - Short name of experiment
 - Expt. Rep ID No.
 - Parameter
 - Value
3. Add a column with reference to correlated utility section?

Svensson, Leonard R.

From: GORMAN, Susan W.
Sent: Wednesday, February 11, 2004 10:11 AM
To: Svensson, Leonard R.
Subject: FW: Pheno_Data000 Table



PHENO_DATA000.doc

Sorry, forgot to attach the file!

-----Original Message-----
From: GORMAN, Susan W.
Sent: Wednesday, February 11, 2004 10:06 AM
To: Svensson, Leonard R.
Subject: Pheno_Data000 Table

Hi Len,

Here is what I have come up with regarding the Phenotype data table

1. Needs reformatting into discrete columns — Sandra working on
2. "Promoter" column
 Do we have descriptors/definitions for 35S, 326D, 34414F, etc?
3. "line_id" column
 are the "-01," "-02," etc. indicative of rep numbers?
 If so, why isn't phenotype observed the same?
 (compare ME05809-01 to ME05809-02)
4. "Phenotype present?" column
 some entries read "Questionable" Keep these in?
 some entries read [NULL]. Is this different from "no" and how?
 (see entry 12348448 in data table attached below)
5. No heading for 5th column
 What are these numbers? (Look like microplate well numbers)
 Are these needed? If so, why?
6. No heading for 6th column
 No entry other than [NULL] here.
 Is this column needed? If so, why?
7. No heading for 7th column
 What are these numbers? What does [NULL] mean in relation to them?
8. Is there a good reason to include all of the data with no phenotype?
 The table description already states that this table records gross, visible phenotypes only